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ORIGINAL INVESTIGATIONS

Effect of Prasugrel Pre-Treatment Strategy in Patients Undergoing Percutaneous Coronary Intervention for NSTEMI

The ACCOAST-PCI Study

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ABSTRACT

BACKGROUND After percutaneous coronary intervention (PCI) for non–ST-segment elevation myocardial infarction (NSTEMI), treatment with a $P2Y_{12}$ antagonist with aspirin is recommended for 1 year.

OBJECTIVES The oral $P2Y_{12}$ antagonists ticagrelor and prasugrel have higher recommendations than clopidogrel, but it is unknown if administration before the start of PCI is beneficial.

METHODS In the randomized, double-blind ACCOAST (A Comparison of prasugrel at the time of percutaneous Coronary intervention Or as pre-treatment At the time of diagnosis in patients with non–ST-segment elevation myocardial infarction) trial, 4,033 patients were diagnosed with NSTEMI and 68.7% underwent PCI; 1,394 received pre-treatment with prasugrel (30-mg loading dose), and 1,376 received placebo. At the time of PCI, patients who received pre-treatment with prasugrel received an additional 30-mg dose of prasugrel, and those who received placebo received a 60-mg loading dose of prasugrel. Primary efficacy was a composite of cardiovascular death, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa bailout through 7 days from randomization. Investigators captured the presence of thrombus on initial angiography and during PCI.

RESULTS The incidence of the primary endpoint through 7 days from randomization in the pre-treatment group versus the no pre-treatment group was 13.1% versus 13.1% ($p = 0.93$). Pre-treatment with prasugrel was not associated with decreases in any ischemic event, including total mortality. Patients with thrombus on angiography had a 3-fold higher incidence of the primary endpoint than patients without thrombus. There was no impact of pre-treatment with prasugrel on the presence of thrombus before PCI or on occurrence of stent thrombosis after PCI. There was a 3-fold increase in all non–coronary artery bypass graft Thrombolysis In Myocardial Infarction (TIMI) major bleeding and a 6-fold increase in non–coronary artery bypass graft life-threatening bleeding with pre-treatment with prasugrel; the same trends persisted in patients who had radial or femoral access even with use of a closure device.

CONCLUSIONS These findings support deferring treatment with prasugrel until a decision is made about revascularization in patients with NSTEMI undergoing angiography within 48 h of admission. (A Comparison of prasugrel at the time of percutaneous Coronary intervention Or as pre-treatment At the time of diagnosis in patients with non–ST-segment elevation myocardial infarction [ACCOAST]; NCT01015287) (J Am Coll Cardiol 2014;64:2563–71) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CI = confidence interval

GP = glycoprotein

HR = hazard ratio

NSTE-ACS = non-ST-segment elevation acute coronary syndrome

NSTEMI = non-ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

TIMI = Thrombolysis In Myocardial Infarction

Optimal antiplatelet therapy is necessary in patients undergoing percutaneous coronary intervention (PCI), although the intensity of treatment and timing of administration are not well defined and may vary according to the clinical presentation. Pre-treatment is defined as treatment administered before coronary angiography. Coronary angiography confirms the diagnosis, defines the coronary status, and provides an indication of the need for revascularization. The main goal of pre-treatment is effective platelet inhibition for patients who require PCI, which is generally performed immediately after coronary angiography. The downside of a systematic strategy of pre-treatment is that it can cause a high level of platelet inhibition in patients who need emergent coronary artery bypass graft (CABG) surgery or unnecessarily increase the risk of bleeding in patients who do not require any intervention.

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In the contemporary era, in which patients have rapid access to the catheterization laboratory, randomized studies of pre-treatment strategies have failed to show a reduction of ischemic events and have reported serious safety issues when compared with strategies of selecting the same antiplatelet therapy once coronary angiography has been performed. This was shown with upstream glycoprotein (GP) inhibitors in non-ST-segment elevation acute coronary syndromes (NSTE-ACS) in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) and EARLY-ACS (Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary

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Syndrome) trials, leading to a class III recommendation for pre-treatment with GP inhibitors in patients with NSTE-ACS (1,2). The deleterious effects of pre-treatment were also shown with clopidogrel in randomized studies evaluating stable or stabilized patients, leading to a class III recommendation for pre-treatment with clopidogrel in these patients (3–6). No randomized studies have evaluated routine pre-treatment versus no pre-treatment with clopidogrel or ticagrelor and invasive management in patients with NSTE-ACS. In contrast, pre-treatment with prasugrel was evaluated with patients with NSTE-ACS scheduled to undergo catheterization in the randomized, double-blind ACCOAST (A Comparison of prasugrel at the time of percutaneous Coronary intervention Or as pre-treatment At the time of diagnosis in patients with non-ST-segment elevation myocardial infarction) trial, which revealed no additional efficacy benefit with routine pre-treatment with prasugrel compared with selective use of prasugrel at the time of PCI but showed an increase in the rate of major bleeding complications (7).

Intracoronary thrombus and thrombotic complications during PCI, in particular in patients with acute coronary syndrome, have been a concern and have led to the concept of pre-treatment with clopidogrel, a drug with a delayed onset of action (8). Although this strategy makes sense for patients undergoing PCI, it was never demonstrated in patients with NSTE-ACS who were invasively managed within 48 h of admission, as performed in contemporary practice. The ACCOAST-PCI study was a unique opportunity to evaluate this concept in the modern era, in which patients have rapid access to the catheterization laboratory, frequent radial access, and access to drug-eluting stents with modern pharmacological therapy, including prasugrel.

METHODS

PARTICIPANTS. The ACCOAST-PCI study prospectively evaluated 2,770 patients undergoing PCI who were randomized to double-blind therapy with prasugrel or placebo at 171 centers in 19 countries (7). The inclusion and exclusion criteria for the ACCOAST trial have been described previously (7,9). Briefly, patients were eligible for inclusion if they had a diagnosis of NSTE-ACS with an elevated troponin level. Randomization was to take place as soon as possible after diagnosis and before the patients received a loading dose of clopidogrel or any dose of prasugrel or ticagrelor. Patients were to be scheduled to undergo coronary angiography within 2 to 48 h from randomization. The ACCOAST study design pre-specified the prospective capture on a specific part of the case report form and the presence of thrombus during the procedure, and additional analyses were performed in relationship to clinical outcomes.

PROCEDURES. In addition to aspirin, patients were randomly assigned to receive either prasugrel or matching placebo once admitted to the study site with a diagnosis of non-ST-segment elevation myocardial infarction (NSTEMI). In the pre-treatment arm, patients received a 30-mg loading dose of prasugrel and an additional 30-mg dose of prasugrel at the time of PCI once angiography confirmed the indication for PCI. In the no pre-treatment arm, the approved 60-mg loading dose of prasugrel was administered after angiography at the time of PCI.

The first open-label maintenance dose of prasugrel was administered 18 to 24 h after PCI. Patients received a 10-mg daily maintenance dose of prasugrel in combination with aspirin through the follow-up visit at 30 days. In patients who were 75 years of age or older and/or had body weight <60 kg, a 5-mg daily maintenance dose of prasugrel was administered.

We routinely screened for periprocedural increases in cardiac enzyme concentrations every 8 h over the first 24 h after PCI. Definitions of myocardial infarction used creatine kinase or creatine kinase-myocardial bands and depended on the clinical timing of the event in relation to the timing of the index event and PCI procedures (9). The definition of urgent revascularization was driven by recurrent signs of ischemia occurring after completion of PCI, leading to a new emergent revascularization (PCI or CABG surgery) of either the vessel dilated at the initial procedure or a vessel not initially dilated. The unplanned use of a GP IIb/IIIa inhibitor while waiting for coronary angiography/PCI, during PCI, or within 24 h after PCI was considered bailout. Investigators documented planned use of a GP IIb/IIIa inhibitor once randomization occurred or before PCI, and this was not considered a GP IIb/IIIa inhibitor bailout endpoint. If Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 to 1 was identified during initial coronary angiography and before PCI that required use of a GP IIb/IIIa inhibitor, a GP IIb/IIIa inhibitor bailout endpoint was reported. Reasons for use of GP IIb/IIIa inhibitor bailout were recorded by the sites, and all cases of GP IIb/IIIa inhibitor bailout were adjudicated.

The primary endpoint was time to first occurrence of cardiovascular death, myocardial infarction, stroke, urgent revascularization, or GP IIb/IIIa inhibitor bailout through 7 days from randomization. Safety endpoints of TIMI major and minor bleeding were evaluated as not related to CABG surgery and all bleeding. Bleeding complications also were

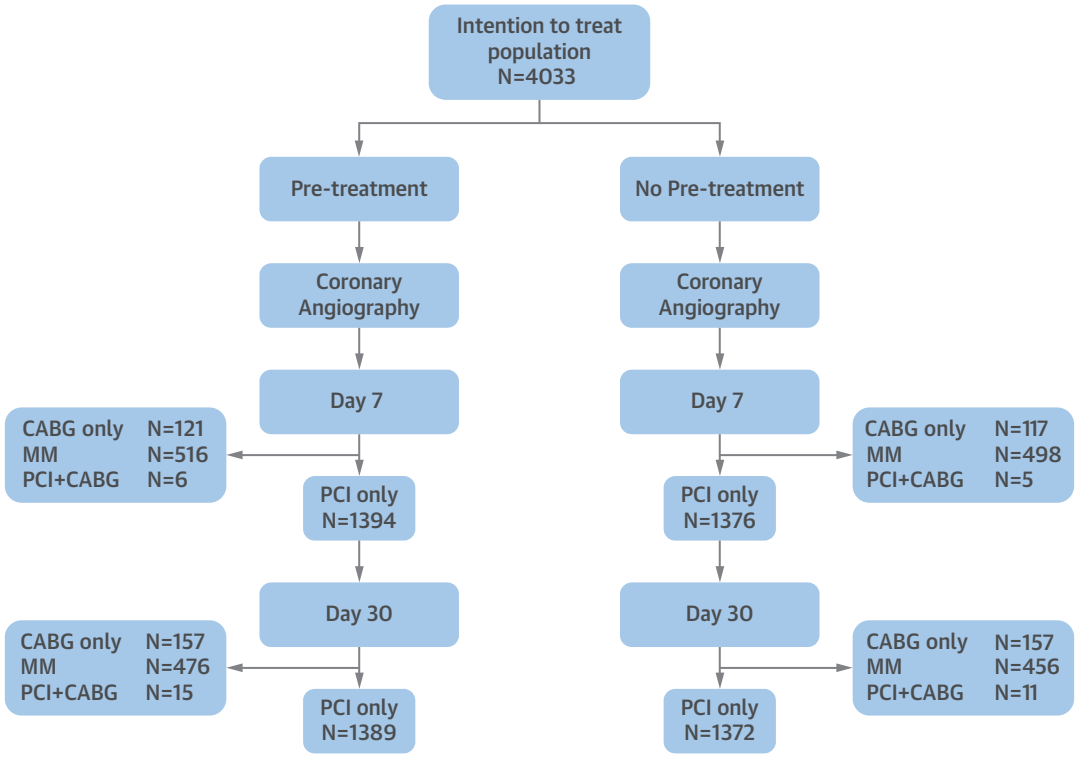
adjudicated according to STEEPLE (Safety and Efficacy of Enoxaparin in PCI) definitions (9). An independent endpoint adjudication committee adjudicated the endpoints.

STATISTICAL CONSIDERATIONS. Comparisons of efficacy were performed on the basis of time to first event, according to intention-to-treat principle (Online Appendix). Safety analyses were performed on all patients who took at least one dose of study drug. Primary efficacy analysis was on the basis of time from randomization to the first occurrence of the primary composite endpoint on the basis of a 2-sided log-rank test. Time-to-event analyses for efficacy and safety outcomes were performed through 7 and 30 days from randomization. Rates are expressed as Kaplan-Meier estimates. An estimated hazard ratio (HR) and 95% confidence interval (CI) were obtained from a Cox proportional hazards model, and a 2-sided p value was obtained by the log-rank test. A p value for efficacy and safety was considered statistically significant when <0.05. Comparisons between patients with and without thrombus on angiography were performed for efficacy outcomes. Additionally, a multivariate stepwise Cox proportional hazards model was performed for the primary efficacy outcome and TIMI major or minor bleeding to investigate which characteristics were independently associated with these outcomes.

RESULTS

DEMOGRAPHIC CHARACTERISTICS. Overall, 2,770 of the 4,033 patients (68.7%) in the ACCOAST trial underwent PCI through 7 days from randomization. Of these, 1,394 patients were assigned to pre-treatment with prasugrel and 1,376 patients were assigned to placebo at baseline. No patients were lost to follow-up (**Figure 1**). The median delay between randomization and PCI was 4.25 h. The 2 groups were balanced with respect to baseline characteristics (Online Table 1). By study design, all patients had an increase in troponin level at randomization; 33% of

FIGURE 1 Patient Flow



A total of 4,033 patients were randomized in the ACCOAST study. A total of 1,394 patients in the pre-treatment group underwent PCI, and 1,376 patients in the no pre-treatment group underwent PCI. CABG = coronary artery bypass graft; MM = medical management; PCI = percutaneous coronary intervention.

patients in both the prasugrel pre-treatment group and no prasugrel pre-treatment group had initial troponin levels ≥3 and <10 times the upper limit of normal, and 51% of patients in both the prasugrel pre-treatment group and no prasugrel pre-treatment group had initial troponin levels ≥10 times the upper limit of normal. Radial access was preferred in 43% of the PCI cohort. Among the patients who had femoral access, a closure device was used in 40%. The characteristics reflect a population that was enrolled before coronary angiography; 4% had left main PCI, 38% had multivessel PCI, 10% had dilation of the 3 vessels, and 13% had long lesions, defined as more than 30 mm of stents. Drug-eluting stents were used most of the time. Importantly, a thrombus was angiographically noted before the start of PCI in 20% and 22% of patients with and without pre-treatment with prasugrel, respectively (p = 0.21). The preferred anticoagulants were unfractionated and low-molecular-weight heparins. Planned and unplanned GP IIb/IIIa inhibitor therapy was used in 15% of patients, with only 5.2% in the prasugrel pre-treatment group and 5.5% in the no prasugrel pre-treatment group in bailout situations (not significant between groups). The duration of the PCI procedure was similar in both groups.

TABLE 1 Efficacy Endpoints Through 7 Days and 30 Days

Endpoint	Pre-Treatment (n = 1,394)	No Pre-Treatment (n = 1,376)	HR (95% CI)*	p Value†
7 days				
CVD, MI, stroke, UR, or GP IIb/IIIa inhibitor bailout	183 (13.1)	180 (13.1)	1.01 (0.82–1.24)	0.93
CVD, MI, or stroke	118 (8.5)	115 (8.4)	1.01 (0.78–1.31)	0.92
Death				
All cause	4 (0.29)	4 (0.29)	NE	NE
CV	4 (0.29)	4 (0.29)	NE	NE
MI	114 (8.2)	108 (7.9)	1.05 (0.80–1.36)	0.75
Stroke	3 (0.22)	5 (0.36)	NE	NE
UR	18 (1.3)	23 (1.7)	0.77 (0.42–1.43)	0.41
GP IIb/IIIa inhibitor bailout	72 (5.2)	76 (5.5)	0.94 (0.68–1.30)	0.70
Definite or probable stent thrombosis	1 (0.07)	3 (0.22)	NE	NE
30 days				
CVD, MI, stroke, UR, or GP IIb/IIIa inhibitor bailout	196 (14.1)	189 (13.8)	1.03 (0.84–1.26)	0.77
CVD, MI, or stroke	128 (9.2)	121 (8.8)	1.05 (0.82–1.34)	0.72
Death				
All cause	11 (0.79)	11 (0.80)	0.96 (0.42–2.23)	0.92
CV	10 (0.72)	11 (0.80)	0.90 (0.38–2.12)	0.81
MI	118 (8.5)	111 (8.1)	1.05 (0.81–1.36)	0.70
Stroke	6 (0.43)	8 (0.58)	0.74 (0.26–2.13)	0.58
UR	26 (1.9)	28 (2.0)	0.92 (0.54–1.57)	0.75
GP IIb/IIIa inhibitor bailout	73 (5.3)	77 (5.6)	0.94 (0.68–1.29)	0.70
Definite or probable stent thrombosis	2 (0.14)	5 (0.36)	NE	NE

Values for pre-treatment and no pre-treatment are n (%). *HRs and 2-sided 95% CIs are from a Cox proportional hazards model with treatment as a fixed effect. †2-sided p value on the basis of the log-rank test. Event rates are raw percents.

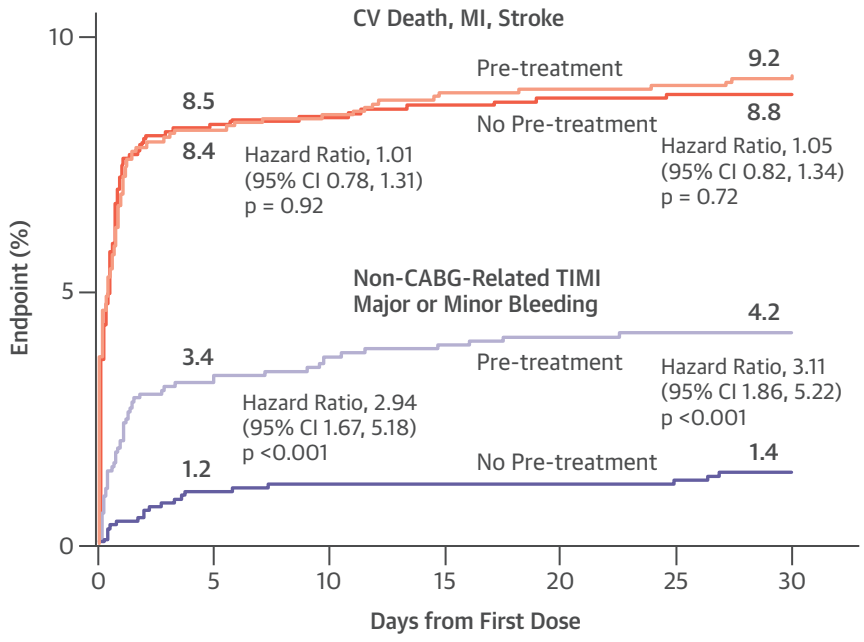
CI = confidence interval; CV = cardiovascular; CVD = cardiovascular death; GP = glycoprotein; HR = hazard ratio; MI = myocardial infarction; NE = not evaluable; UR = urgent revascularization.

OUTCOMES. The incidence of the primary endpoint through 7 days from randomization was not different between the prasugrel pre-treatment group and the no prasugrel pre-treatment group (13.1% vs. 13.1%; p = 0.93) (**Table 1**). The main secondary endpoint of cardiovascular death, myocardial infarction, or stroke did not differ between the 2 groups (**Central Illustration**, **Table 1**). Pre-treatment with prasugrel was not associated with a decrease in any ischemic event, including total mortality and stent thrombosis (**Table 1**).

Bailout use of GP IIb/IIIa inhibitors was infrequent (5% of patients) and did not differ between the 2 randomized groups (**Table 1**). Four of those 10 patients received GP IIb/IIIa inhibitors because of a slow flow before PCI was started, and the other 6 patients received GP IIb/IIIa inhibitors because of a slow flow or another complication during PCI. There was no difference between the prasugrel pre-treatment group and the no prasugrel pre-treatment group regarding the use of GP IIb/IIIa inhibitors either before or during PCI. The reasons for bailout use of GP IIb/IIIa inhibitors are reported in Online Table 2.

The baseline characteristics of patients with and without thrombus on angiography are shown in Online Table 3 and do not appear to differ. However, patients who had thrombus on angiography had a 3-fold higher incidence of 7-day and 30-day primary endpoints than patients without thrombus on angiography (Online Table 4). Surprisingly, there was no impact on the rate of definite or probable stent thrombosis in patients with thrombosis seen on angiography versus patients with thrombus not seen on angiography (Online Table 4). The results of the multivariate analysis indicated that thrombus on angiography was highly predictive of the primary efficacy outcomes (HR: 2.61 [95% CI: 2.09 to 3.25]; p < 0.001), adjusting for all other known significant predictors. Additional significant predictors included length of procedure (HR: 1.88 [95% CI: 1.49 to 2.36]; p < 0.001), number of lesions (HR: 1.24 [95% CI: 1.10 to 1.39]; p < 0.001), maximum length of stent (HR: 1.19 [95% CI: 1.04 to 1.35]; p = 0.005), and CRUSADE risk score (HR: 1.01 [95% CI: 1.00 to 1.02]; p = 0.023) (for every 1-point increase in CRUSADE risk score, the risk increases 1%) but not other baseline demographic and clinical characteristics or GRACE score.

CENTRAL ILLUSTRATION **Efficacy and Safety Endpoints in Patients Undergoing PCI**



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Pre-treatment with prasugrel (30 mg before PCI and 30 mg at the time of PCI) had no effect on the triple efficacy endpoint (cardiovascular death, myocardial infarction, or stroke) compared with no pre-treatment with prasugrel (60 mg at the time of PCI). Pre-treatment with prasugrel showed a 3-fold increase in the incidence of non-coronary artery bypass graft Thrombolysis In Myocardial Infarction (TIMI) major or minor bleeding compared with no pre-treatment. Patients received a 10 mg dose of prasugrel as daily maintenance through day 30. Numerical results are shown for 7 days of treatment and 30 days of treatment. CABG = coronary artery bypass graft; CV = cardiovascular; MI = myocardial infarction; PCI = percutaneous coronary intervention.

ADVERSE EFFECTS. The incidence of TIMI major bleeding through 7 days from the first loading dose was significantly higher with pre-treatment with prasugrel (Table 2); this was also true for TIMI major or minor bleeding (Central Illustration, Table 2). There was a 3-fold increase in non-CABG major bleeding and a 6-fold increase in non-CABG life-threatening bleeding events (Table 2). The most common locations of TIMI major bleeding through 7 days were vascular access sites (n = 9), gastrointestinal (n = 5), pericardial (n = 4), and retroperitoneal (n = 4). The incidence of TIMI minor bleeding events was also increased with pre-treatment with prasugrel (28 [2.01%] vs. 9 [0.65%]). Through 30 days, there were no additional vascular access site or retroperitoneal TIMI major bleeds, but there were 4 additional gastrointestinal bleeds and an additional pericardial major bleed. Rates of total transfusions were significantly higher in patients who received pre-treatment with prasugrel at 7 and 30 days (Table 2).

Rates of TIMI major bleeding were higher in patients who received pre-treatment with prasugrel with both radial and femoral access. Through 7 days, TIMI major bleeding events in patients with radial access were numerically higher with pre-treatment with prasugrel (4 vs. 1; HR: 3.82 [95% CI: 0.43 to 34.15]; p = 0.197). Through 7 days, TIMI major or minor bleeding events in patients with radial access was also numerically higher with pre-treatment with prasugrel (7 [1.15%] vs. 2 [0.34%]; HR: 3.35 [95% CI: 0.70 to 16.10]; p = 0.109). Through 7 days, TIMI major bleeding events in patients with femoral access and use of a closure device were numerically higher with pre-treatment with prasugrel (6 vs. 2; p = 0.180). Through 7 days, TIMI major or minor bleeding events in patients with femoral access and a closure device were higher with pre-treatment with prasugrel (18 [5.84%] vs. 3 [1.03%]; HR: 5.81 [95% CI: 1.71 to 19.7]; p = 0.001). Fourteen of the 18 TIMI major or minor bleeding locations were at the vascular access

site or retroperitoneal. Through 7 days, TIMI major bleeding events in patients with femoral access and without a closure device were numerically higher with pre-treatment with prasugrel (9 [1.90%] vs. 4 [0.80%]; HR: 2.40 [95% CI: 0.74 to 7.79]; p = 0.132). TIMI major or minor bleeding events in patients with femoral access without a closure device were higher with pre-treatment with prasugrel (22 [4.65%] vs. 11 [2.20%]; HR: 2.16 [95% CI: 1.05 to 4.45]; p = 0.033). Thirteen of the 22 TIMI major or minor bleeding events with pre-treatment with prasugrel were at the vascular access site or retroperitoneal bleeding. Multivariate analysis for TIMI major bleeding identified femoral (vs. radial) access (HR: 3.01 [95% CI: 1.13 to 8.00]; p = 0.027) and treatment group (HR: 2.77 [95% CI: 1.16 to 6.60]; p = 0.022) as the 2 strongest independent correlates of bleeding complications.

TABLE 2 Bleeding Endpoints Through 7 Days and 30 Days

	Pre-Treatment	No Pre-Treatment	HR (95% CI)*	P Value†
7 days	(n = 1,394)	(n = 1,376)		
All CABG or non-CABG TIMI major bleeding events (key safety endpoint)	19 (1.4)	7 (0.51)	2.69 (1.13–6.40)	0.02
Non-CABG TIMI major bleeding events	19 (1.4)	7 (0.51)	2.69 (1.13–6.40)	0.02
Fatal bleeding	0 (0)	0 (0)	NE	NE
Life-threatening bleeding	12 (0.86)	2 (0.15)	5.93 (1.33–26.5)	0.008
Location of non-CABG TIMI major bleeding‡				
ICH	0 (0)	0 (0)	NE	NE
Vascular access site	7 (0.50)	2 (0.15)	NE	NE
GI	2 (0.14)	3 (0.22)	NE	NE
Hematuria	1 (0.07)	0 (0)	NE	NE
Pericardial	3 (0.21)	1 (0.07)	NE	NE
Other§	5 (0.36)	1 (0.07)	NE	NE
Non-CABG TIMI major/minor bleeding	47 (3.4)	16 (1.2)	2.94 (1.67–5.18)	<0.001
Total transfusion‖	20 (1.4)	7 (0.5)		0.0131
STEEPLE major (non-CABG)	35 (2.5)	14 (1.0)	2.49 (1.34–4.63)	0.003
STEEPLE minor (non-CABG)	48 (3.4)	35 (2.5)	1.36 (0.88–2.10)	0.166
30 days	(n = 1,389)	(n = 1,372)		
All CABG or non-CABG TIMI major bleeding events	24 (1.7)	9 (0.66)	2.65 (1.23–5.69)	0.010
Non-CABG TIMI major bleeding events	24 (1.7)	9 (0.66)	2.65 (1.23–5.69)	0.010
Fatal bleeding	2 (0.14)	0 (0)	NE	NE
Life-threatening bleeding	17 (1.2)	3 (0.22)	5.61 (1.64–19.13)	0.002
Location of non-CABG TIMI major bleeding‡				
ICH	0 (0)	1 (0.07)	NE	NE
Vascular access site	7 (0.50)	2 (0.15)	NE	NE
GI	4 (0.29)	5 (0.36)	NE	NE
Hematuria	1 (0.07)	0 (0)	NE	NE
Pericardial	4 (0.29)	1 (0.07)	NE	NE
Other§	6 (0.44)	1 (0.07)	NE	NE
Non-CABG TIMI major/minor bleeding	59 (4.3)	19 (1.4)	3.11 (1.86–5.22)	<0.001
Total transfusion‖	26 (1.9)	11 (0.8)		0.0145
STEEPLE major (non-CABG)	45 (3.2)	18 (1.3)	2.49 (1.44–4.31)	<0.001
STEEPLE minor (non-CABG)	61 (4.4)	46 (3.4)	1.32 (0.90–1.93)	0.157

Values for pre-treatment and no pre-treatment are n (%). *HRs and 2-sided 95% CIs are from a Cox proportional hazards model with treatment as a fixed effect. †Two-sided p value on the basis of the log-rank test. ‡Participants experiencing more than 1 bleeding event may be included in more than 1 TIMI bleeding category. Within each TIMI category, locations are reported for the first TIMI bleed in the category. §Other for 7 days included retroperitoneal, respiratory tract, and unknown. Other for 30 days included retroperitoneal, surgical incision site, respiratory tract, and unknown. ‖Transfusion includes any transfusion, fresh frozen plasma, packed red blood cells, platelets, and whole blood cells. The p value was calculated using chi-square test. Event rates are raw percents.

CABG = coronary artery bypass graft; GI = gastrointestinal; ICH = intracranial hemorrhage; STEEPLE = Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention (PCI) Patients, an International Randomized Evaluation; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

DISCUSSION

Patients with NSTEMI who are undergoing PCI theoretically represent the ideal population for pre-treatment with a $P2Y_{12}$ antagonist because they have a thrombotic index event, their coronary anatomy is defined, and they have an indication of coronary stenting with dual antiplatelet therapy. However, our study showed that there was no additional benefit with pre-treatment with prasugrel compared with administration of prasugrel at the time of PCI to reduce the ischemic primary and main secondary endpoints in the NSTEMI population. Moreover, earlier administration of prasugrel was not associated with less thrombus burden at the time of the procedure, less stent thrombosis, or less urgent revascularization and did not decrease the use of GP inhibitors, which remained low in this double-blind study. In contrast, pre-treatment with prasugrel caused a significant excess of major bleeding complications, a risk not eliminated by radial access or the use of a closure device after femoral access. Pre-treatment with prasugrel was a strong correlate of major bleeding and major or minor bleeding independently of other variables, including vascular access.

The concept of pre-treatment with $P2Y_{12}$ antagonists in patients with NSTE-ACS comes from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study, in which patients were managed conservatively with a further benefit suggested in the subgroup of 21% of patients who underwent PCI with or without stent implantation on average 6 days after randomization (10,11). The PCI meta-analysis, on the basis of the subsets of 2 randomized studies performed 15 years ago, showed a 22% relative risk reduction of major adverse cardiac events balanced with a 28% relative increase in major bleeding and no mortality benefit (5). Therefore, the potential benefit of pre-treatment with clopidogrel in patients with NSTE-ACS undergoing PCI is difficult to claim from these data and even more difficult to extend to

modern practice, in which most patients are rapidly and invasively managed. The PCI cohort of patients enrolled in the ACCOAST study was a pre-specified subgroup that reflects modern practice of management of acute coronary syndrome, including early revascularization, and was larger than the PCI-CURE (Percutaneous Coronary Intervention in the Clopidogrel in Unstable Angina to Prevent Recurrent Events) cohort. Indeed, our patients were rapidly managed in the catheterization laboratory, with large use of radial access and closure devices; significant numbers of long lesions, left main, and multivessel stenting; and treatment with a predominance of drug-eluting stents. Although patients could undergo angiography up to 48 h from randomization, the median time to angiography was shorter, which is similar to what has been observed in contemporary studies of acute coronary syndrome (12–16).

The ACCOAST investigators noted prospectively the presence of thrombus on angiography because they were blinded to study drug, and 21% of patients were found to have an intracoronary thrombus. Visually, there was no patient characteristic, including the GRACE score or any coronary characteristic, that was predictive of the presence of thrombus in these patients who had a significant increase in troponin levels at admission. Pre-treatment with prasugrel did not reduce the presence of thrombus before the start of the PCI procedure and did not reduce the thrombotic complications during the procedure. However, the angiographic presence of thrombus drove the use of GP inhibitors (8-fold increase) and was associated with more frequent urgent revascularization (3-fold increase), more frequent myocardial infarctions (50% increase), and altogether a 2.5-fold increase in the incidence of the primary endpoint.

The multivariate analysis of the primary efficacy outcome concludes that lesion- or stent-related characteristics predict outcome, and the presence of thrombus was the stronger variable in this model. The ACCOAST study reinforces the role of angiography to diagnose NSTEMI, indicate the need for PCI, and avoid pre-treatment with prasugrel when it is not required. The ACCOAST-PCI study shows that there is no downside in waiting to provide prasugrel until after coronary angiography in patients who will need dual antiplatelet therapy for stenting. The angiogram provides additional information on the risk of the procedure and the prognosis for these patients. Although PCI was performed in patients who had an increase in troponin levels, with frequent long or multiple lesions and a high rate of thrombus-containing lesions, the rate of GP IIb/IIIa inhibitor use remained low and stent thrombosis was infrequent in both arms. This suggests that the strategy of prasugrel loading after angiography is not only safer but also effective in this population.

STUDY LIMITATIONS. Although our study was pre-specified, its limitations include the fact that the original effects of randomization at entry into the trial are no longer present for the cohort of patients who have undergone PCI. To alleviate this issue, we presented the baseline characteristics of the patients, which were well balanced between the 2 groups. Moreover, it would be practically impossible to perform a randomized study of pre-treatment only in patients undergoing PCI, knowing that more than 90% of patients undergo ad-hoc PCI (in the same setting as angiography). Another limitation is the time frame from randomization to PCI (2 to 48 h), and our results apply only to patients with rapid access to the catheterization laboratory. The negative results from pre-treatment with prasugrel in the NSTEMI population in the ACCOAST study cannot be applied to the ST-segment elevation myocardial infarction population. The ATLANTIC (A 30 Day Study to Evaluate Efficacy and Safety of Pre-hospital vs. In-hospital Initiation of Ticagrelor Therapy in STEMI Patients Planned for Percutaneous Coronary Intervention [PCI]) trial (NCT01347580) will provide answers to the question of the use of pre-hospital treatment with a $P2Y_{12}$ inhibitor in the ST-segment elevation myocardial infarction population (17). Finally, whether our conclusions can be extended to other oral $P2Y_{12}$ antagonists will remain a matter of debate because no similar study has been performed in the same conditions with ticagrelor or clopidogrel. Considering the recent reappraisal of pre-treatment with clopidogrel, we advise caution with pre-treatment.

CONCLUSIONS

In patients with NSTEMI, our data support deferring a loading dose of prasugrel until a decision is made about revascularization. This strategy allows flexibility in the management of patients by providing prasugrel, with its rapid onset of action, to patients who proceed to PCI without risking bleeding complications in patients who do not proceed to PCI.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with NSTEMI and a thrombus burden face increased rates of adverse events compared with those without a thrombus burden.

COMPETENCY IN PATIENT CARE: Patients with NSTEMI face an increased risk of bleeding when pre-treated with a rapid-onset $P2Y_{12}$ platelet inhibitor.

TRANSLATIONAL OUTLOOK: These results support delaying a loading dose of prasugrel until a decision is made about revascularization because of increases in all non-CABG major and life-threatening TIMI bleeding events without reduction of ischemic events associated with pre-treatment with prasugrel in patients with NSTEMI.

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KEY WORDS acute coronary syndromes(s), percutaneous coronary intervention, prasugrel

APPENDIX For supplemental tables, please see the online version of this article.